The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed R. Mahoney

Dated 8 September 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
25 JUL 2002
RECEIVED BY HAND

The Patent Office

26 E736212-3 D00524
P01/7700 0.00-0217306.0

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference — **4-32584P1**

2. Patent application number — **0217306.0**
(The Patent Office will fill in this part) — **25 JUL 2002**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **SWITZERLAND**

7125487005

4. Title of invention — **Compositions Comprising Organic Compounds**

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Novartis Pharmaceuticals UK Ltd
Patents and Trademarks
Wimblehurst Road
HORSHAM
West Sussex
RH12 5AB
ADP No. 07185220021

Patents ADP number *(if you know it)*

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description	21
Claim(s)	7
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B. A. Yorke & Co. Date

B.A. Yorke & Co. 25 July 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

Compositions Comprising Organic Compounds

The present invention relates to pharmaceutical compositions for sustained release comprising as active ingredient an HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, said composition comprising an inner phase (internal) and an outer phase (external), wherein at least the outer phase comprises at least one matrix former. When using the composition according to the present invention, unexpected advantages can be demonstrated.

The term "modified", "extended" "sustained release" hereinbefore and herafter shall corresponds to an active ingredient that is released from the dosage form over an extended period of time, for example more than about four hours. Preferably, the pharmaceutical compositions should release after ingestion in vivo an amount of drug substance which corresponds in vitro to at least 80 weight percent of the active agent after eight hours, with the balance of the pharmaceutically active agent being released thereafter. In preferred compositions, less than about 15 weight percent of the pharmaceutically active agent is released in vitro in the first 0.5 hour, from about 10 to about 50 weight percent of the pharmaceutically active agent is released within about 2 hours, and from about 40 to about 70 weight percent of the pharmaceutically active agent is released within about 4 hours.

It has been surprisingly found that the composition according to the invention more advantageously increases the distribution of the HMG-CoA reductase inhibitor to the liver due to the slow drug release and decreases the drug plasma levels and consequently the distribution to the muscle tissue. The consequence is a better tolerability as compared to the tolerability of the same dose of an immediate release composition of the HMG-CoA reductase inhibitor. Because of the improved tolerability of the extended release composition higher doses can be administered leading to with higher efficacy of the drug. The improved tolerability of the pharmaceutical composition and consequently higher efficiacy, due to the possibility to administer higher doses, according to the invention is based on a well adaptated extended release profile. An improved adapted extended release profile is due notably to the presence of the matrix former of different viscosities in both the inner and external phase of the composition according to the present invention and is also due to the adequate distribution between the inner and/or outer (external) phase, creating an

advantageous diffusion barrier by hydrogel formation of the matrix in aqueous media. Furthermore, a small size of the pharmaceutical dosage form and, in parallel, the possibilty to apply a low dose formulation of active ingredient induce a better tolerability of the active ingredient.

HMG-CoA reductase inhibitors, also called β-hydroxy-β–methylglutaryl-co-enzyme-A reductase inhibitors and also called statins) are understood to be those active agents which may be preferably used to lower the lipid levels including cholesterol in blood and can be used e.g. for the prevention or treatment of hyperlipidemia and artheriosclerosis.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features.

HMG-CoA reductase inhibitor compounds are disclosed, e.g., in the following commonly assigned patents, published patent applications and publications which are all hereby incorporated herein by reference:

Specific examples of compounds disclosed in the above publications, which are HMG-CoA reductase compounds suitable to be employed as the drug active agent in the compositions of the invention, comprise the following sodium salts, or other pharmaceutically acceptable salts:
(E)-(3R,5S)-7-[2-Cyclopropyl-4-(4-fluoro-phenyl)-quinolin-3-yl]-3,5-dihydroxy-hept-6-enoic acid, calcium salt;
3R,5S-(E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-2- dimethylaminopyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
erythro-(±)-(E)-7-[3-(4-fluorophenyl)-spiro[cyclopentane-1,1'-1H- inden]-2'-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
3R,5S- (E)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-indolizin-2-yl]-3,5-dihydroxy- 6-heptenoic acid, sodium salt;
3R,5S-(E)-7-[3-(4-fluorophenyl)-1- (1-methylethyl)-1H-pyrrolo[2,3-b] pyridin-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
3R,5S-(E)-7-[4-(4-fluorophenyl)-2-(1- methylethyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[1-(4-fluorophenyl)-3-(1-methylethyl)-4-oxo-1,4- dihydroquinolin-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4-fluorophenyl)-6-(1-methylethyl)-3-methyl-1H- pyrazolo [3,4-b]pyridin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[3-(1-methylethyl)-5,6-diphenyl-pyridazin-4-yl]-3,5- dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4- fluorophenyl)-6-(1-methylethyl)-2-phenyl-pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4-fluorophenyl)-1- (1-methylethyl)-3-phenyl-2-oxo-2,3-dihydroimidazol-5-yl]-3,5-dihydroxy-6- heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4-fluorophenyl)-2- (1-methylethyl)-1-oxo-1,2-dihydro-quinolin-3-yl]-3,5-dihydroxy-6- heptenoic acid, sodium salt;

erythro-(±)-(E)-7-[4-(4-fluorophenyl)-2-(1-methylethyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

erythro- (±)-(E)-7-[1-(4-fluorophenyl)-3-(1-methylethyl)-pyrrolo [2,1- a]isoquinolin-2-yl]-3,5-dihydroxy-6-heptenoic acid sodium salt;

erythro-(±)-(E)-7-[4-cyclopropyl-6-(4-fluorophenyl)-2-(4- methoxyphenyl)pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4-fluorophenyl)-2,6-dimethylpyrimidin-5-yl]-3,5- dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(4- fluorophenyl)-6-methyl-2-phenyl-pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4-(3,5-dimethylphenyl)-6-methyl- 2-phenyl-pyrimidin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

erythro-(±)-(E)-7-[3,4-bis(4-fluorophenyl)-6-(1-methylethyl)- pyridazin-5-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

erythro-(±)-(E)-7-[1-(4-fluorophenyl)-3-(1-methylethyl)-5-phenyl-1H- pyrrol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

erythro-(±)-(E)-9,9-bis(4-fluorophenyl)-3,5-dihydroxy-8-(1-methyl-1H- tetrazol-5-yl)-6,8-nonadienoic acid, sodium salt;

erythro-(±)- (E)-3,5-dihydroxy-9,9-diphenyl-6,8-nonadienoic acid,sodium salt;

erythro-(±)-(E)-7-[4-(4-fluorophenyl)-1,2-bis(1-methylethyl)-3- phenylpyrrol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;

3R,5S-(E)-7-[4,5-bis(4-fluorophenyl)-2-(1-methylethyl)-1H- imidazol-1-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
3R, 5S-(E)-7-[4-(4-fluorophenyl)-2,6-bis(1-methylethyl)-5-methoxymethyl- pyridin-3-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
erythro-(±)-(E)-[4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenyl-pyridin-3- yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
erythro-(±)-(E)- [2-(4-fluorophenyl)-4,4,6,6-tetramethyl-cyclohexen-1-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt;
erythro-(±)-(E)-7-[4-(4- fluorophenyl)-2-cyclopropyl-quinolin-3-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt; and
erythro-(±)-(E)-7-[4-(4-fluorophenyl)-2-(1- methylethyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt.

Preferred are compounds which are selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, nisvastatin, pitavastatin (formerly itavastatin), pravastatin, rosuvastatin, and simvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

Especially preferred HMG-Co-A reductase inhibitors are those agents which have been marketed. Most preferred are atorvastatin, fluvastatin, nisvastatin, pitavastatin or simvastatin or a pharmaceutically acceptable salt thereof, in the first line pitavastain or a pharmaceutically accetpable salt thereof.

Only salts that are pharmaceutically acceptable and non-toxic are used therapeutically and those salts are therefore preferred.

The corresponding active ingredient or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The structure of the active agents identified hereinbefore or hereinafter by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agent and, based on these references, likewise

enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

In a preferred embodiment of the present invention the amount of an HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 5 to 50 % by weight of the composition.

In an especially preferred embodiment of the invention the amount of an HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 10 to 20 % by weight of the composition.

In an especially preferred embodiment of the invention the amount of an HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 1-32mg, preferably 1-16mg per dosage unit form.

Preferably, hydrophilic, non-ionic, slowly swelling and gel forming polymers are employed as matrix former. This type of polymers exhibit different swelling characteristics and therefore different viscosities in aqueous media and form upon ingestion of the solid dosage form different diffusion barriers (the matrix) releasing the drug substance by rate-controlled diffusion. A substantial amount of the released active agent may be processed efficiently at the targeted active site. The polymer is present in an amount providing sufficient strength to the gel matrix to prevent its premature degradation. The gel matrix should also be formed within a time period that is effective to prevent the premature release of the active agent.

For example, the gel matrix preferably forms within about 5 minutes after ingestion of the composition to prevent a burst of active agent prior to gel formation. It is believed that the nonionic, hydrophilic polymer operates to decrease the rate of gel formation to an acceptable level. The non ionic, hydrophilic polymer may be present in the pharmaceutical composition in an amount ranging from about 1 to about 60 weight percent, preferably from about 15 to about 50 % by weight of the dosage unit form, preferably from about 18 to about 40 % by weight of the dosage unit form.

A matrix former, for example, is a substance selected from the group consisting of a hydroxypropyl methyl cellulose (HPMC or hypromellose); hydroxypropylcellulose ;

hydroxymethylcellulose; polyethylene glycols; polyethylene and co-polymers thereof; polyvinylpyrrolidone; polyvinyl alcohol; furthermore selected from the group consisting of polysaccharides such as alginate; carrageenan; scleroglucan; pullulan; dextran; haluronic acid; chitin; chitosan; starch; further natural polymers such as proteins, for example, albumin or gelatine; natural rubber; furthermore selected from the group consisting of synthetic polymers such as acrylates, for example, polymethacrylate, poly(hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(hydroxy ethyl methacrylate-co-methyl metacrylate, Carbopol 934 ™; polamides such as polyacrylamide or poly(methylene bis acrylamide); polyanhydrides such as poly(biscarboxyphenoxy)methane; PEO-PPO block-co-polymers such as poloxamers; polyvinylchloride, polyvinyl pyrrolidone, polyvinyl alcohol; polyethylene; polyethylene glycols and co-polymers thereof; polyethylene oxides and co-polymers thereof; polypropylene and co-polymers thereof; polystyrene; polyesters such as poly(lactic acid), poly(glycolic acid), poly(caprolactone) and co-polymers thereof,nylon; poly(ortho esters and co-polymers thereof; resins such as Dowex ™ or Amberlite ™; polycarbonate; cellophane; silicones such as poly(dimethylsiloxane); polyurethanes; synthetic rubbers such as styrene butadiene rubber or isopropene rubber; furthermore selected from the group consisting of waxes such as carnauba wax, beeswax, glycowax or castor wax; stearates such as glycerol palmitostearate, glyceroyl monostearate, glyceryl tristearate or stearyl alcohol; lipids such as glycerides or phospholipids; and paraffin.

In a most preferred embodiment of the present invention an HPCM is selected as matrix former.

In a preferred embodiment of the present invention the pharmaceutical compositions comprise from about 1 to about 60 % by weight HPMC of the dosage unit form, preferably from about 1 to 15 % by weight HPMC of the dosage unit form, more preferably from about 18 to about 40 % by weight HPMC of the dosage unit form.

The HPCM components have viscosities of approximately 100 to approximately 100'000 cps (viscosities values given of 2% aqueous solutions of the HPMC types.).

According to the invention, the matrix former of the internal and /or external phase may comprise one or more type(s) of matrix former(s) having different viscosities.

Preferably, the matrix former of the external phase comprises one or more type of matrix former component having different viscosities.

In a preferred embodiment of the present invention the HPMC polymer(s) used as matrix former of the inner phase has a viscosity of about 4 to about 500 cps, preferably of about 4 to about 250 cps, more preferably about 100 cps.

In a preferred embodiment of the present invention the viscosities of the HPMC polymer(s) used as matrix former of the external phase are of about 100 to about 100000cps, preferably of about 100 to 50000cps, more preferably of about 100 to 25000cps.

Furthermore the invention relates a corresponding composition, wherein one type of HPMC polymer(s) used as matrix former component of the external phase has a viscosity of about 80 to 150 cps and another type of HPMC polymer(s) used as matrix former component has a viscosity of about 50000 to 100000 cps.

In a preferred embodiment the invention the viscosities of the HPMC polymer(s) used as matrix former in the external phase range from approximately 100 to approximately 100'000 cps.

In a preferred embodiment, the total amount of the matrix forming HPMC component(s) having a viscosity of about 100 cps ranges from about 10-35 mg per dosage unit form.

In a preferred embodiment, the total amount of the matrix forming HPMC component(s) having a viscosity of about 100'000 cps ranges from about 10-35 mg per dosage unit form.

In another especially embodiment of the invention is a composition, the matrix forming HPMC components are selected from the group consisting of Methocel K100 Premium LVCR EP (100cps) and Methocel K100M Premium CR EP (100000cps).

The ratio between HPMC polymers contained in the "internal phase" (granulate) and the external phase, i.e., excipients admixed to the granulate after the drying/screening process is comprised between 0:100 and 100:0.

The composition according to the present invention furthermore may also comprise a stabilizer, especially for protecting the drug substance adequately against pH-related destabilization.

Additionally, the heat and light sensitivity as well as hygroscopicity of an active ingredient impose particular requirements on the manufacture and storage of pharmaceutical dosage forms.

Certain HMG-CoA reductase inhibitors are extremely susceptible to degradation at pH below about 8. An example of such a compound comprises the compound having the USAN designation fluvastatin sodium (hereinafter "fluvastatin"), of the chemical designation: R*,S*-(E)-(±)-7-[3-(4-fluorophenyl)-1-(1-methyl-ethyl)-1H-indol-2-yl]-3,5- dihydroxy-6-heptenoic acid, sodium salt, [see European Patent Application EP-A-114027].
For example, it has been found the degradation kinetics of fluvastatin in aqueous solution at various pH are as illustrated below:

% fluvastatin remaining at 37°C

pH	after 1 hour	after 24 hrs
7.8	98.3	98.0
6.0	99.6	97.1
4.0	86. 7	25.2
1.0	10.9	0

The above-indicated instability of fluvastatin and related HMG-CoA reductase compounds is believed to be due to the extreme lability of the β, δ-hydroxy groups on the heptenoic acid chain and the presence of the double bond, such that at neutral to acidic pH, the compounds readily undergo elimination or isomerization or oxidation reactions to form conjugated unsaturated aromatic compounds, as well as the threo isomer, the corresponding lactones, and other degradation products.

In order to achieve marketable dosage forms comprising such a compound, it is essential to adequately protect it against pH-related destabilization.

A preferred stablizer to be used according to the present invention is an "alkaline medium", said alkaline medium being capable of stabilizing the composition by imparting a pH of at least 8 to an aqueous solution or dispersion of the composition. Since the stabilizer is added in solution during the aqueous granulation process, it is in intimate contact with the active ingredient in the composition to achieve optimal stability of the medicament.

The term "alkaline medium" or "base" employed herein shall refer to one or more pharmaceutically acceptable substances capable of imparting a pH of at least 8, and preferably at least 9, and up to about pH 10, to an aqueous solution or dispersion of the composition of the invention. More particularly, the alkaline medium creates a "micro-pH" of at least 8 around the particles of the composition when water is adsorbed thereon or when water is added in small amounts to the composition. The alkaline medium should otherwise be inert to the compounds of the formulas. The pH may be determined by taking a unit dosage of the composition containing e.g. 4 mg of pitavastatin or the equivalent amount of another compound and dispersing or dissolving the composition in 10 to 100 ml of water.
The pharmaceutically acceptable alkaline substance(s) which comprise the alkaline medium may range from water-soluble to sparingly soluble to essentially water-insoluble.

In a preferred embodiment of the present invention, the stabilizer is a basic stabilizer selected from the group consisting of inorganic water-soluble or inorganic water-insoluble compound.

An inorganic water-soluble compound is a suitable carbonate salt such as sodium or potassium carbonate, sodium hydrogen or bi carbonate, potassium hydrogen or bi carbonate; phosphate salts selected from, e.g., anhydrous sodium, potassium or calcium dibasic phosphate, trisodium phosphate; alkali metal hydroxides, selected from sodium, potassium, or lithium; and mixtures thereof.

Sodium or potassium bicarbonate advantageously serves to neutralize acidic groups in the composition in the presence of moisture that may adsorb onto particles of the composition during storage. The calcium carbonate exerts a buffering action in the stored composition, without apparent effect on drug release upon ingestion.It has further been found that the carbonate salts sufficiently stabilize the drug substance such that conventional water-based

preparative techniques, e.g. trituration with water or wet granulation, can be utilized to prepare stabilized compositions of the invention.

Examples of water-insoluble compound are suitable alkaline compounds capable of imparting the requisite basicity include certain pharmaceutically acceptable inorganic compounds commonly employed in antacid compositions (e.g., magnesium oxide, hydroxide or carbonate; magnesium hydrogen carbonate; aluminum or calcium hydroxide or carbonate; composite aluminum-magnesium compounds, such as magnesium aluminum hydroxide); as well as pharmaceutically acceptable salts of phosphoric acid such as tribasic calcium phosphate; and mixtures thereof.

The proportion of a particularly stabilizing excipient to be employed will depend to some extent on the intended manufacturing process. In compositions to be tableted, for example, calcium carbonate should not exceed a proportion which can no longer be conveniently subjected to compression, and will generally be used in combination with a more readily compressible alkaline substance, e.g., sodium bicarbonate. On the other hand, capsule dosage forms may comprise higher levels of poorly compressible excipients, provided that the overall composition remains sufficiently free-flowing and processible.

A solid unit dosage composition may have the ratio of water soluble carbonate to insoluble carbonate from e.g 1:40 to 2:1.

An exemplary tablet of the invention may comprise a ratio between calcium carbonate and sodium bicarbonate of about 2:1 to 1:2 by weight. A capsule composition may comprise these excipients in a ratio of, for example 25:1 to 35:1 by weight.

An example of a stabilized composition according to the invention may comprise: 0.5 to 40 wt. %, of the active ingredient (e.g., pitavastatin); and preferably 0.1 to 35 wt.%, more preferably 1-15 wt.%, of soluble carbonate compound used as a stabilizer, for example, selected from potassium bicarbonate, potassium carbonate and/or mixtures thereof.

In a preferred embodiment, the amount of stabilizer is from about 0.1-10 mg per dosage unit. It is a further advantage that the stabilized compositions of the invention can be readily prepared by aqueous or other solvent-based techniques, e.g. wet granulation.

The composition according to the present invention may furthermore comprise a filler. In addition to the drug substance and alkaline medium, a filler is also generally employed in the compositions to impart processability. Suitable filler materials are well-known to the art (see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990), Mack Publishing Co., Easton, PA, pp. 1635-1636), and include microcrystalline cellulose (e.g., Avicel PH101 and /or Avicel PH102),lactose and other carbohydrates, starch, pregelatinized starch, e.g., starch 1500R (Colorcon Corp.), corn starch, dicalcium phosphate, potassium bicarbonate, sodium bicarbonate,cellulose, calcium phosphate dibasic anhydrous, and mixtures thereof, of which lactose, microcrystalline cellulose, pregelatinized starch, and mixtures thereof, are preferred.

Owing to its superior disintegration and compression properties, microcrystalline cellulose (Avicel, FMC Corp.), and mixtures comprising microcrystalline cellulose and one or more additional fillers, e.g., pregelatinized starch, are particularly useful.
The total filler is present in the compositions in an amount of about 1 to 65 wt.%, based on the total composition, preferably 20 to 60 wt%, more preferably 50wt%.
The invention relates to compositions wherein the filler consists of microcrystalline cellulose.

The composition according to the present invention may comprise further components which may be incorporated to facilitate processing and/or provide enhanced properties of the product dosage form, include well-known tableting binders (e.g., hydroxypropylmethyl-cellulose, starch, starch pregelatinized (starch 1500) ,gelatin, sugars, natural and synthetic gums, such as carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, low substituted hydroxypropylcellulose, ethylcellulose, polyvinylacetate, polyacrylates, gelatin, natural and synthetic gums), microcrystalline cellulose, and mixtures of the foregoing); disintegrants (e.g., cross-linked carboxymethyl- cellulose, croscarmelose, crospovidone, sodium starch glycolate), lubricants (e.g., magnesium stearate, stearic acid, calcium stearate, glyceryl behenate, hydrogenated vegetable oil, carnauba wax and the like); flow agents (e.g., silicon dioxide, talc, polyethylene oxides), anti-adherents or glidants (e.g., talc) as well as sweeteners, coloring mediums (e.g., iron oxide, aluminum lakes), flavoring mediums, antioxidants, etc. Selection of a particular ingredient or ingredients and the amounts used will be readily determinable by one skilled in the art by reference to standard procedures and practices for preparing tableted or encapsulated or other dosage forms. In general, an

effective amount of a tableting binder will comprise about 1 to 10 wt.%, and preferably 1 to 5 wt.%; anti-adherents or glidants, about 1 to 10 wt.%; disintegrants, about 1 to 5 wt.%, and lubricants, about 0.1 to 2 wt.%, based on the total composition. The invention relates to formulations wherein the binder consists of hydroxypropylmethyl-cellulose (HPMC) of lower viscosities , e.g., 3 or 6 cps, preferably 3 cps without or in combinations with HPC.

The composition according to the present invention may furthermore comprise film coating components to protect against moisture and light discoloration, and to mask the bitter taste of the drug.
Examples of suitable film formers in film coating compositions to be applied to compositions of the invention comprise, e.g., polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydrophilic polymers such as hydroxypropylcellulose, hydroxymethylcellulose, and hydroxypropylmethylcellulose or the like, of which hydroxypropylmethylcellulose (e.g., Methocel 3 cps (Dow) or preparations as Opadry , Colorcon Corp.) are preferred.

Enteric film coating components may optionally be applied to oral tablets, pellets or capsules to protect against premature degradation of the drug substance by gastric acid prior to reaching the intestinal absorption site. Examples of such materials are well-known and include hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, methylcellulose phthalate, copolymerized methacrylic acid/methacrylic acid methyl esters (e.g., EudragitR, Rohm Pharma). The enteric coating is preferably applied to result in about a 5 to 12, preferably 8 to 10, weight percent increase of the capsule, pellet or tablet core.

A conventional opaque film coating may be applied to the tablet core, optionally after it has been coated with an enteric substance.

Hydrophobic film-formers which may be applied using an organic solvent vehicle comprise, for example, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, etc.

The film coating may be generally applied to achieve a weight increase of the pellet or core or tablet of about 1 to 10 wt.%, and preferably about 2 to 6 wt.%.

Other film coating composition ingredients include plasticizers, e.g., polyethylene glycol (e.g. polyethylene glycol 6000), triethylcitrate, triacetin, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, in conventional amounts, as well as the above- mentioned opacifiers such as titanium dioxide, and colorants, e.g. iron oxide, aluminum lakes, etc.

The film coatings can be applied by conventional techniques in a suitable coating pan or fluidized bed apparatus using water and/or conventional organic solvents (e.g., methyl alcohol, ethyl alcohol, isopropyl alcohol), ketones (acetone, ethylmethyl ketone), chlorinated hydrocarbons (methylene chloride, dichloroethane), etc.

As previously indicated, an enteric and/or film coating composition can be applied to the dosage form for its particular benefits.
Enteric or film coating of a microcrystalline cellulose-based tablet with a water-based film coating composition is desirably carried out at a bed temperature of 30-50°C., an inlet temperature of 50-80°C. and a relative humidity (RH) of less than 50%.

The resulting tableted or capsule dosage forms should be protected during storage against thermal or light induced oxidation as well as moisture contamination.

According to the invention, there is provided a composition, wherein the ratio between the matrix former in the internal and external phase is from about 0.0:1 to 10:1,preferably from 0.01:1 to 1:0 most preferably from 0.01:1 to 5:1,

The present invention relates to compositions wherein the ratio between HPMC 100 cps and HPMC 100'000 cps is from about 1:0 to 0:1.

Furthermore the invention relates to a composition wherein the ratio between HPMC 100 cps and HPMC 100'000 cps of the external phase is from about 1:0 to 0:1, preferably 1/1.

Furthermore the invention relates to a composition wherein the ratio between HPMC100cps intern and the HMG CoA reductase inhibitor calcium salt is from about 0.1:1 to 10:1

The invention particularly relates to compositions wherein the ratio between the matrix forming HPMC in the internal phase and the total weight, is from approx. 0:8 to 2:3.

The invention particularly relates to a composition wherein the ratio between the total HPMC in the internal phase and the total weight, is from about 0.01:1 to 0.8:1

The invention particularly relates to compositions wherein the ratio between the matrix forming HPMC in the external phase and the total weight is from approx. 0:8 to 2:3.

The invention particularly relates to a composition wherein the ratio between the total HPMC in the external phase and the total weight, is from about 0.01:1 to 0.8:1

The invention particularly relates to compositions wherein the ratio between the total amount of matrix forming HPMC and the total weight, is from approx. 1:2 to approx. 1:6

The present invention is concerned with compositions wherein the ratio between the total amount of matrix forming HPMC and the HMG CoA reductase inhibitor is from approx. 1:1 to 10:1, preferably 6:1.

According to the invention, there are provided compositions wherein the ratio between the matrix forming HPMC in the internal phase and the HMG CoA reductase inhibitor is from 0 to approx10:1, preferably approx 6:1.

According to the invention, there are provided compositions wherein the ratio between the matrix forming HPMC in the external phase and the HMG CoA reductase inhibitor is from 0 to approx.10:1, preferably 6:1.

The present invention is concerned with a composition wherein the ratio between the filler in the internal phase and the HPMC comprised in the internal phase is about from 0.5:1 to 20:1, preferably from 0.5:1 to 10:1

The invention relates to a composition wherein the ratio between the filler in the external phase and the HPMC comprised in the external phase is about from 0 to 1/1

The invention relates to a composition wherein the ratio between the filler in the internal phase and the HPMC total is about from 0.1 to 1/1.

The invention also relates to a composition wherein the ratio between the filler in the external phase and the HPMC total is about from 0 to 1/1.

To obtain very stable compositions, an aqueous or other solvent-based preparative process is preferably utilized, whereby the drug substance and alkaline medium are blended together in the presence of minor amounts of, e.g., water, to provide particles containing the drug and alkaline substance in intimate admixture.

In another embodiment of an aqueous or a solvent-based process which can be assisted by subsequent drying in a fluidized bed, the drug substance and alkaline medium are wet granulated by known techniques, i.e. blended in the moistened state, together with an amount of the filler material. The thus-formed granules, after drying, are then combined with the external phase, e.g, any remaining filler and other excipients, e. g., binder, lubricant, and can therefore be tableted, encapsulated, or otherwise shaped into a dosage form.
Drying is conventionally performed by tray drying or in a fluidized bed, preferably the latter.

Pharmaceutical compositions, e.g. oral dosage forms, according to the invention may be formulated in any conventional form, e.g. powders, granules / granulates, capsules or tablets. Preferred pharmaceutical compositions may be in the form of tablets.

Such compositions may be formulated by known means to provide standard unitary oral dosages of compound, e.g., 4 mg, 8 mg, 12 mg, 16 mg, etc., as e.g., powders, granulates, capsules, pellets or tablets.

A special embodiment of the invention relates to tablet having a diameter from 6 to 8 mm having a weight between 80 to 180 mg wherein the active ingredient have a weight between 4 and 40 mg per dosage unit form, preferably between 8 and 16 mg.

Pharmaceutical compositions, e.g. oral dosage forms, hereinabove described may be formed of a granulated mass comprising fluvastatin, HPMC and optionally other excipients commonly used in pharmaceutical composition, e.g. oral dosage forms, e.g. tablets.

Various dissolution profiles of different strengths can therefore be obtained either by compressing the same tabletting mixture to tablets of dose proportional weights or by maintaining the same tablet size/weight over all dosage strengths (weight compensation by the excipient used as filler).

The pharmaceutical compositions according to the invention can be prepared by use of well known pharmaceutical processing techniques such as blending, granulation, milling, spray drying, compaction, or coating, e.g the manufacturing procedure of the pharmaceutical composition, e.g oral dosage forms, can, for example, be described in the following steps:

- Place the drug substance, HPMC (binder, low viscosity), HPMC or different HPMC qualities (matrix former, high viscosity) and microcrystalline cellulose (powder) into the bowl of the high shear mixer (remark: the matrix former may be omitted, according the the actual composition).
- Mix (e.g., 5 minutes)
- Dissolve Potassium bicarbonate in purified water
- Add the solution to the mixture (2)
- Rinse the container of step (3) with purified water and add the rinsing liquid to the mixture of step (4)
- Mix/knead/granulate the compounds.
- Screen the wet granulate (e.g, a sieve of 2 mm mesh size).
- Dry the granulate on trays or in a fluid bed dryer (preferred).
- Screen the dried granulate into the container of a free fall mixer (e.g., a sieve of 1 mm mesh size).
- Mix HPMC or different HPMC qualities (matrix former, high viscosity), microcrystalline cellulose (granular) and colloidal silicon dioxide in the free fall mixer (remark: the microcrystalline cellulose (granular) may be omitted according to the actual composition).
- Screen magnesium stearate to the mixture of step (10).
- Mix the components of step (11).

- Compress the tabletting mixture of step (12) on a force feeding (rotary) tabletting machine to tablets (or tablet cores, if film coating is necessary) of the required weight and dimensions.
- (optional) Add the prepared dry powder blend for the film coat preparation (e.g, Opadry) to purified water
- (optional) Stir the mixture until a homogeneous dispersion/solution is obtained
- (optional) Spray the suspension of step (15) on the cores of step (13) until the required weight of the film coat is achieved.

An alternative (generic) manufacturing procedure of the pharmaceutical composition, e.g oral dosage forms can be described in the following steps :

- Place the drug substance, the matrix former(s) (or combinations of them), the disintegrant(s) (if requested) and the filler(s) (if requested, also other excipients as listed below the table 1) into the bowl of the high shear mixer (remark: the matrix former may be omitted, according the the actual composition).
- Mix (e.g., 5 minutes)
- Dissolve the stabilizer in purified water
- Add the solution to the mixture (2)
- Rinse the container of step (3) with purified water and add the rinsing liquid to the mixture of step (4)
- Mix/knead/granulate the compounds.
- Screen the wet granulate (e.g, a sieve of 2 mm mesh size).
- Dry the granulate on trays or in a fluid bed dryer (preferred).
- Screen the dried granulate into the container of a free fall mixer (e.g, a sieve of 1 mm mesh size).
- Mix the matrix former(s), filler(s), disintegrant(s), glidant(s)/flow agent(s) (if requested, also other excipients as listed below the table 1) in the free fall mixer (remark: the matrix former(s) may be omitted according to the actual composition).
- Screen the lubricant(s) to the mixture of step (10) or prepare a premix of the lubricant(s) with a small part of the mixture (10) and screen this lubricant(s) premix to the remaining part of mixture (10).
- Mix the components of step (11).

- Compress the tabletting mixture of step (12) on a force feeding (rotary) tabletting machine to tablets (or tablet cores, if film coating is necessary) of the required weight and dimensions.
- (optional) Add the film formers to the required liquid (solvent(s mixtures) or purified water) and dissolve the film former. Add plasticizer(s), if required.
- (optional) Prepared a suspension of the coloring agent(s) and titanium dioxide (white pigment) in the required liquid.
- (optional) Add the suspension of step (15) to the solution of step (14).
- (optional) Stir the mixture until a homogeneous dispersion/solution is obtained
- (optional) Spray the suspension of step (17) on the cores of step (13) until the required weight of the film coat is achieved.

A composition according to the invention comprises (in weight percent based on the total composition):

Drug substance: approx. 5-50 wt % of the formulation; preferably 10-20 wt %

Matrix former: The amount of HPMC as matrix former is between 15 and 50 wt %, preferably 18-40 wt %

Stabilizer (alkaline medium): 1-15 wt %

Filler: About 1 to 65 wt %, preferably about 20-60 wt %, more preferably approx. 50 wt %

Example 1:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, for example pitavastatin Ca-salts,, 46.67 wt% of microcrystalline cellulose, 3.13 wt% of HPMC (3 cps), 1.25 wt% of potassium bicarbonate, the external phase comprising 37.5 wt% HPMC (100'000 cps), 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 2:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts,, 46.67 wt % of microcrystalline cellulose, 3.13 wt % of HPMC (3 cps), 1,25 wt % of potassium bicarbonate, the external phase comprising 18.75 wt % HPMC (100'000 cps), 18.75 wt % HPMC (100 cps), 0.5 wt % of silicium dioxide colloidal and 0.5 wt % of magnesium stearate.

Example 3:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts,, 46.67 wt % of microcrystalline cellulose, 3.13 wt % of HPMC (3 cps), 1,25 wt % of potassium bicarbonate, the external phase comprising 37.5 % HPMC (100 cps), 0.5 wt % of silicium dioxide colloidal and 0.5 wt % of magnesium stearate.

Example 4:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 44.8 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 18.75 wt% HPMC (100 cps) 1,25 wt % of potassium bicarbonate, the external phase comprising 18.75 wt % HPMC (100'000 cps), 0.5 wt % of silicium dioxide colloidal and 0.5 wt % of magnesium stearate.

Example 5:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 33.8 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 37.5 wt% HPMC (100 cps) 1,25 wt% of potassium bicarbonate, the external phase comprising 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 6:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 51.05 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 31.25 wt% HPMC (100 cps) 1,25 wt% of potassium bicarbonate, the external phase comprising 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 7:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts,, 26.05 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 18.75 wt% HPMC (100 cps) 1,25 wt % of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100'000 cps), 18.75 wt% of microcrystalline cellulose, 0.5 wt % of silicium dioxide colloidal and 0.5 wt % of magnesium stearate.

Example 8:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 26.05 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 18.75 wt% HPMC (100 cps) 1,25 wt % of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100'000 cps), 18.75 wt% of microcrystalline cellulose , 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 9:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 39.8 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 5 wt% of HPC, 18.75 wt% HPMC (100 cps) 1,25 wt% of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100'000 cps), 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 10:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 39.8 wt% of microcrystalline cellulose, 5 wt% of HPMC (3 cps), 5 wt% of HPC, 18.75 wt% HPMC (100 cps) 1,25 wt% of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100 cps), 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 11:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 46.67 wt% of microcrystalline cellulose, 3.13 wt% of HPMC (3 cps), 1,25 wt% of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100'000 cps), 18.75 wt% microcrystalline cellulose, 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

Example 12:

Inner phase:10.45 wt% of drug substance –alkaline medium, for example pitavastatin Ca-salts, 46.67 wt% of microcrystalline cellulose, 3.13 wt% of HPMC (3 cps), 1,25 wt% of potassium bicarbonate, the external phase comprising 18.75 wt% HPMC (100 cps), 18.75 wt% microcrystalline cellulose, 0.5 wt% of silicium dioxide colloidal and 0.5 wt% of magnesium stearate.

The above example are intended to illustrate the invention in various of its embodiments without being limitative in anyway thereof.

The present invention also relates to a pharmaceutical composition for the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated comprising an HMG CoA reductase inhibitor or a pharmaceutically acceptable salt thereof and a matrix former, wherein said composition comprises an internal and an external phase wherein at least the outer phase comprises a matrix former.

The present invention also relates to amethod of treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated comprising administering to a patient in need thereof atherapeutically effective amount of a composition according to the invention.

The present invention also concern a method of releasing a pharmaceutically active agent in a mammal, wherein the method includes orally administering the pharmaceutically active agent to the mammal as part of a composition according to the invention.

The present invention also concern the use of the composition according to the invention in the manufacture of a medicament for use in the treatment or prevention of a cardiovascular disease, e.g, hypercholesterolemia, hyperproteinemia and /or atherosclerosis.

In a preferred embodiment the invention relates to the use of the composition according to the invention in the manufacture of a medicament wherein said medicament is a hypercholesteremic, hyperlipoproteinemic or anti-atherosclerotic agent.

What is claimed is

1. An pharmaceutical compositions for sustained release comprising as active ingredient an HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, said composition comprising an inner phase (internal) and an outer phase (external), wherein at least the outer phase comprises at least one matrix former.

2. A composition according to claim 1, wherein the HMG CoA reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

3. A composition according to claim 2, wherein the HMG CoA reductase inhibitor is pitavastatin or a pharmaceutically acceptable salt thereof.

4 A composition according to claim 1 wherein the amount of HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 5-50 weight % of the composition.

5 A composition according to claim 1 wherein the amount of HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof is about 10-20 weight % of the composition

6 A composition according to claim 1 wherein the HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof amount is about 1-32mg

7 A composition according to claim 1 wherein the HMG CoA reductase inhibitor or pharmaceutically acceptable salt thereof amount is about 1-16mg

8 A composition according to claim 1, wherein the matrix former of the inner phase comprises one or more types of matrix former component having different viscosities.

9 A composition according to claim 1, wherein the matrix former of the external phase comprises one or more type of matrix former component having different viscosities.

10 A composition according any one of claims 1 to 9, wherein the matrix former is selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydrophilic polymers such as hydroxypropylcellulose, hydroxymethylcellulose, and hydroxypropylmethylcellulose or the like.

11 A composition according to claim 10, wherein the matrix former is hydroxypropylmethylcellulose (HPMC).

12 A composition according to claim 11, wherein the HPMC is selected from the group consisting of: Methocel K100M Premium CR EP (100000cps) and Methocel K100 Premium LVCR EP (100cps).

13 A composition according to claim 1, wherein the matrix former of the inner phase has a viscosity of about 4 to about 500 cps.

14 A composition according to claim 13, wherein the matrix former of the inner phase has a viscosity of about 4 to about 250 cps.

15 A composition according to claim 14, wherein the matrix former of the inner phase has a viscosity of about 100 cps.

16 A composition according to claim 1, wherein the matrix former of the external phase has a viscosity of about 100 to about 100000cps.

17 A composition according to claim 16, wherein the matrix former of the external phase has a viscosity of about 100 to 50000cps.

18 A composition according to claim 17, wherein the matrix former of the external phase has a viscosity of about 100 to 25000cps.

19 A composition according to claim 1, wherein one type of HPMC used as a matrix former component of the external phase has a viscosity of about 80 to 150 cps and the other type of of HPMC used as a matrix former component has a viscosity of about 50000 to 100000 cps.

20 A composition according to claim *1* wherein the amount of HPMC used as a matrix former is about 1-60 weight % of the composition.

21 A composition according to claim 1 wherein the amount of HPMC used as a matrix former is about 18-40 weight % of the composition.

22 A composition according to claim 12 wherein the HPMC 100cps used as matrix former amount is from about 10-35 mg

23 A composition according to claim 12 wherein the HPMC 100000cps amount used as matrix former is from about 10-35mg.

24 A composition according to any one of claims 1 to 23, wherein the ratio between the matrix former in the internal and external phase is from about 0,01/1 to 10/1 .

25 A composition according to claim 1 to 24, wherein the ratio between the matrix former in the internal and external phase is from about 0.01/1 to 5/1.

26 A composition according to claim 1 to 25 wherein the ratio between the matrix former in the internal and external phase is from about 0.01/1 to 1/0.

27 A composition according to claims 1-26, wherein the ratio between the matrix forming HPMC total and the HMG CoA reductase inhibitor is from approx. 1:1 to 6:1

28 A composition according to claim 8 wherein the ratio between the total matrix forming HPMC in the internal phase and the total weight, is from about 0.01/1 to 0.8/1

29 A composition according to claim 8 wherein the ratio between the matrix forming HPMC in the internal phase and the total weight, is from approx. 0:8 to 2:3.

30 A composition according to claim 9 wherein the ratio between the total HPMC in the external phase and the total weight, is from about 0.01/1 to 0.8/1

31 A composition according to claim9, wherein the ratio between the matrix forming HPMC in the external phase and the total weight is from approx. 0:8 to 2:3.

32 A composition according to claim11 wherein the ratio between the total HPMC and the total weight, is from about 0.01/1 to 0.8/1

33 A composition according to claim11 wherein the ratio between the HPMC intern total and the HMG CoA reductase inhibitor calcium salt is from about 0.01/1 to 10/1

34 A composition according to claim1 wherein the ratio between the matrix forming HPMC in the external phase and the HMG CoA reductase inhibitor calcium salt is from 0 to approx. 6:1

35 A composition according to claim12 wherein the ratio between the HPMC100cps intern and the HMG CoA reductase inhibitor calcium salt is from about 0.1/1 to 10/1

36 A composition according to claim12 wherein the ratio between the HPMC total and the HMG CoA reductase inhibitor is from about 0.5/1to 10/1

37 A composition according to claim12, wherein the ratio between the matrix forming HPMC in the internal phase and the HMG CoA reductase inhibitor is from 0 to approx. 6:1

38 composition according to any one of claims12, wherein the ratio between the total amount of matrix forming HPMC and the total weight, is from approx. 1: 2 to approx. 1: 6

39 A composition according to claim1 wherein the internal phase and /or the external phase comprises a filler.

40 A composition according to claim 39 wherein the filler consists in microcrystalline cellulose

41 A composition according to claim 39 wherein the filler consists in Avicel PH101 and /or Avicel PH 102

42 A composition according to claim 39 wherein the amount of the filler is about 20-60 weight % of the composition.

43 A composition according to claim 39 wherein the amount of the filler is about 50 weight % of the composition.

44 A composition according to claim 39 wherein the filler amount is about 30-40mg per dosage unit.

45 A composition according to claim 39, wherein the total amount of the filler is from about 20-40 mg per dosage unit

46 A composition according to claim39 wherein the ratio between the filler and the HPMC comprised in the internal phase is about from 0 to 20/1.

47 A composition according to claim 39 wherein the ratio between the filler in the internal phase and the HPMC comprised in the internal phase is about from 0.5/1 to 10/1.

48 A composition according to claim 39 wherein the ratio between the filler in the external phase and the HPMC comprised in the external phase is about from 0/1 to 1/1

49 A composition according to claim 39 wherein the ratio between the filler in the internal phase and the HPMC total is about from 0.1/1 to 5/1 .

50 A composition according to claim 39 wherein the ratio between the filler in the external phase and the HPMC total is about from 0/1 to 1/1.

51 A composition according to claim 1, wherein said composition comprises a stabilizer (alkaline medium).

52 A composition according to claim 51, wherein the stabilizer is a basic one selected from the group consisting of inorganic carbonate salts such as sodium or potassium carbonate, sodium bicarbonate, potassium hydrogen carbonate; phosphate salts selected from, e.g., anhydrous sodium, potassium or calcium dibasic phosphate, trisodium phosphate; alkali metal hydroxides sodium, selected from potassium, or lithium hydroxide; and mixtures thereof.

53 A composition according to claim 52, wherein the stabilizer is potassium bicarbonate.

54 A composition according to claim 51, wherein the amount of the stabilizer is about 1-15 weight % of the composition.

55 A composition according to claim 51 wherein the amount of stabilizer is from about 0.1-10 mg per dosage unit.

56 A composition according to any one of claims 1 to 55 in form of a tablet.

57 A tablet according to claim A composition according to 56 having a diameter from 6 to 8 mm and a weight between 80 to 160 mg.

58 A composition according to any of the preceding claim defined with reference to the examples.

59 A method of treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated comprising administering to a patient in need thereof atherapeutically effective amount of a composition according to any one of claims 1 to 58.

60 A pharmaceutical composition for the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated comprising an HMG CoA reductase inhibitor or a pharmaceutically acceptable salt thereof and a matrix former, wherein said composition comprises an internal and an external phase wherein at least the outer phase comprises a matrix former.

61 A method of releasing a pharmaceutically active agent in a mammal, wherein the method includes orally administering the pharmaceutically active agent to the mammal as part of a composition according to any one of claim 1 to 58.

62 Use of the composition according to any one of claim 1 to 58 in the manufacture of a medicament for use in the treatment or prevention of a cardiovascular disease, e.g, hypercholesterolemia, hyperproteinemia and /or atherosclerosis.

63 Use according to claim 62 wherein said medicament is a hypercholesteremic, hyperlipoproteinemic or anti-atherosclerotic agent.